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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,391	HIRST, TIMOTHY RAYMOND	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,10-12,17,18,21 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10-12,17,18,21 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph T. Woitach** and the group art unit is now **1632**.

Applicants' amendment filed July 13, 2006, has been received and entered. Claims 4-9, 13-16, 19, 20, 22-25 have been canceled. Claims 1-3, 12, 17, 18 and 21 have been amended. Claim 26 has been added. Claims 1-3, 10-12, 17, 18, 21 and 26 are pending.

Election/Restrictions

The restriction requirement of 12/8/2005 was withdrawn in part. Specifically, Examiner has withdrawn the requirement for Applicant to elect either a mutant form or EtxB or a mutant form of CtxB as put forth on page 3 of the restriction requirement.

In the response of 2/9/2006 Applicant has elected group I and has elected the agent identified as peptide or protein of interest. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)). The restriction requirement was made FINAL.

Newly added claim 26 depends on claim 21 and recites an optional element originally presented in claim 21, thus is encompassed by the elected invention.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in The United Kingdom on 6/22/2001. It is noted, however, that applicant has not filed a certified copy of the 01153823.4 application as required by 35 U.S.C. 119(b).

Applicants indicate that an additional priority filing is not required for a PCT application, citing MPEP 201.11(a). See page 6 of Applicants' amendment.

Applicants' comments are noted, however appear to be in part incorrect. Examiner would agree that filing under 371 provides benefit to the PCT application, however this does not provide sufficient support for the claim to a foreign priority document. Specifically, 35 USC 365 provides the requirements for claim of a foreign priority document, referencing 35 USC 119(a). In this case, a certified copy of the foreign application is required to establish the claim for priority for the claimed invention.

Specification/Drawings

The specification is objected to because page 46, Table I lists peptides longer than 10 amino acids that are not properly identified by a SEQ ID NO.

It is noted that Applicants have not responded to this objection in their remarks or by amendment to the specification.

The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and

1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

In addition to table I on page 46, it is noted that the figure legends and figures comprise reference to protein and nucleic acid sequences.

Appropriate correction is required throughout the disclosure.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

Claim Objections

Claims 1, 12, 14, 15, 17 and 21 objected to because of the following informalities: the terms EtxB and CtxB are not defined at the first recitation of said terms is withdrawn.

Amendment to the claims has addressed the objection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 17 rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101 is withdrawn.

Amendments to the claims have addressed the basis of the rejection by setting forth at least one active step. It is noted that the rejection was in part incorrect, because while previously incomplete as a method the product itself had utility under 35 USC 101.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 10-12, 17, 18, 21 stand rejected and newly added claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

An *in vitro* method of delivering a peptide to a cell expressing GM-1 ganglioside receptors on the surface of said cell comprising contacting said cell with a mutant B-subunit of *E. coli* heat labile enterotoxin (EtxB) or a mutant B-subunit of *Vibrio cholerae* cholera toxin (CtxB) covalently linked to said peptide, said mutant EtxB or mutant CtxB comprising one of the following point mutations within the region spanning amino acid residues E51 to I58 of the β 4-α2 loop of EtxB or CtxB: CtxB(E51A), CtxB(Q56A), CtxB(H57A) and EtxB(H57S), thereby delivering said peptide into said cell; and a kit comprising said mutant EtxB or mutant CtxB covalently linked to said peptide; does not reasonably provide enablement for a method of delivering any agent to any target cell comprising contacting said cell with any mutant EtxB or any mutant CtxB, thereby delivering said agent to said cell resulting in treatment of the breadth of disorders and diseases encompassed by the claims.

Applicant notes the amendments to the claims and outline the embodiments now required by the claims (see page 7-8). More specifically, it is argued that the method is not a method of treatment of a disorder or disease (see page 8)-noting that claims drawn to treating specific diseases has been cancelled (page 8). Applicant's comments have been fully considered, but not found persuasive.

Examiner would agree that the amendments have addressed the rejection in part, however have failed to address the basis of the rejection completely. Initially it is noted that the claims specifically setting forth treatment of diseases and disorders have been cancelled, however this does not address the issue regarding the breadth of the claims as pending. A review of the teachings of the present specification teaches that the purpose for delivery is for treatment. There is no other use enabled by the present specification for a general delivery method. Moreover, it is noted that while certain claims have been cancelled, claim 3 has been amended to recite and encompass delivery of specific antigens only consistent with the intent to treat a subject. Additionally, claim 12 recites making a "medicament" clearly indicating the intent of the product made.

As noted previously, the specification contemplates that the compositions of the present invention can be administered by direct injection, parenteral, muscoal, intramuscular, intravenous, subcutaneous, intraocular or transdermal administration (page 25, lines 4-12). The specification discloses laundry lists of delivery vehicles (page 25, lines 7-12) and of disorders and/or diseases to be treated by the claim methods (page 26, line 22 to page 27, line 10). For example, the specification recites a long list of infectious diseases to be treated including HIV-1

and HIV-2 (page 26, line 26) and a long list of cancers to be treated including melanoma and breast cancer (page 27, lines 7 and 9). As summarized in the previous office action, Plant et al **(Current Topics in Medicinal Chemistry, 4:509-519, 2004)** teaches the state of the art and reviews the teachings of Bergerot and Sun (page 512). Plant recognizes first, that antigens must be conjugated to toxin B subunits in order to elicit a biological response. The teachings of Bergerot and Sun, and said teachings as summarized by Plant, indicate that toxin B subunits must possess immunomodulatory activity and must be conjugated to antigens in order to mediate a biological response in animal models of autoimmune disorders. As such, an artisan would experience undue experimentation to practice the claimed invention, for example, to elicit a biological response in animal models of autoimmune disorders, because it would be unpredictable whether mutant EtxB/CtxB lacking immunomodulatory activity would be operant and it would be unpredictable whether antigens or agents not conjugated to EtxB/CtxB would work. More generally, Michl *et al.* was cited for the teaching of the state of art in bacterial toxins as therapeutic agents for cancer. Michl teaches that several hurdles remain in the art of treating cancer with bacterial toxins as immunomodulators and delivery vehicles for antigens/proteins of interest including targeting to cancer cells and maintaining efficacious levels of said antigens/proteins to be delivered to said cancer cells.

The amendment to the claims is noted, however the instant claims still read on CtxB/EtxB mutants containing <u>any</u> mutations within the region spanning amino acid residues E51 to I58 of the loop of EtxB or CtxB. The breadth of the instant claims encompass any point mutation, any mutation that results in truncation of the CtxB/EtxB protein at any one of amino acid residues E51 to I58 or any mutation that deletes one or more amino acids within the region

spanning amino acid residues E51 to I58. Dependent claim 10 further limits said mutation to a mutation at amino acid residues 51, 56 and/or 57 of the □4-□2 loop and dependent claim 11 further limits said mutation to wherein the mutant comprises a H57A or H57S mutation. The specification discloses alanine scanning mutagenesis of all residues within the region from E51 to I58 (page 33) but only discloses that EtxB(H57A) covalently conjugated to a 19mer peptide stimulated class I-restricted antigen presentation when incubated with cultured JAWS II cells (page 56). Williams et al. teaches several CtxB/EtxB mutants including CtxB(E51A), CtxB(V52A), CtxB(P53A), CtxB(G54A), CtxB(S55A), CtxB(Q56A), CtxB(H57A), CtxB(I58A) and EtxB(H57S) (Examples 1 and 2, pages 40-43) but that only molecules with point mutations at three separate sites (positions 51, 56 and 57; i.e. CtxB(E51A), CtxB(Q56A), CtxB(H57A) and EtxB(H57S)) retain GM-1 binding activity (page 12, lines 20-21). It is reiterated, as put forth herein above, that the art of record at the time of the invention clearly teaches that EtxB/CtxB binds to GM-1 on the surface of cells and that said binding mediates cellular uptake of EtxB/CtxB. As such, it is unpredictable whether CtxB/EtxB mutants containing any mutations within the region spanning amino acid residues E51 to I58 of EtxB or CtxB or whether any mutations at amino acid residues 51, 56 and/or 57 of the loop of EtxB or CtxB would bind GM-1 and be operant in the instantly claimed invention. The specification provides no specific guidance or working examples for an artisan to make and use the claimed invention commensurate with the instant claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and

whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

In summary, it is maintained that an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of delivering any peptide or protein of interest to a target cell without conjugating said peptide of protein of interest directly to EtxB/CtxB, because of the unpredictability of targeting EtxB/CtxB to any cell, including cells not expressing GM-1, because of the unpredictability of any mutant EtxB/CtxB binding to GM-1 and because of the unpredictability of treating any disease or disorder, including any viral infection or any cancer, comprising targeting an agent, peptide, protein of interest or antigen to a target cell with a mutant EtxB/CtxB. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 10-12, 17, 18, 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Amendment to the claims have addressed the basis of the specific rejections.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 10, 11, 17 and 21 stand rejected and newly amended claims 18 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams *et al.*

Applicant argues that while Williams *et al.* teach some of the physical requirements of the claims regarding the delivery of antigens go GM-1 containing cells with mutant forms of EtxB, it fails to teach that the delivery is to the MHC claim antigen processing pathway. See Applicant's amendment, page 8. Applicant's arguments have been fully considered, but not found persuasive.

Examiner would acknowledge that Williams *et al.* does not teach that the antigen will be processed through the MHC class I processing pathway, however provides all the physical requirements of the claims regarding the use of mutant EtxB and antigen, and delivery to the cell. Any property of this composition and practicing this method would inherently provide. With respect to the method of making a product in claim 12, clearly Williams *et al.* provides the

methods, and in this case the intended use of making fails to distinguish the process of making the same product.

Newly added claim 26 requires only a means for detection, which is very broad encompassing any means. In this case, a functional assay to determine the antigen is present on the surface, as evidenced by its consequence affect in an animal of a CTL response anticipates the claims.

As noted previously, Williams teaches mutant B-subunits of Etx and Ctx; specifically, CtxB(E51A), CtxB(V52A), CtxB(P53A), CtxB(G54A), CtxB(S55A), CtxB(Q56A), CtxB(H57A), CtxB(I58A) and EtxB(H57S) (Examples 1 and 2, pages 40-43). Said CtxB/EtxB mutants all contain point mutations in the region spanning amino acid residues E51 to I58 of the □4-□2 loop of CtxB/EtxB. Williams teaches that CtxB(E51A) and CtxB(H57A) failed to trigger CD8+ T-cell depletion (Example 1, Results, page 41). Williams teaches that all of said CtxB/EtxB mutants bound to CD8+ T-cells to a similar extent and that both CtxB(H57A) and EtxB(H57S) bound with a slightly higher avidity to GM-1 coated microtitre plates and exhibited a slightly higher K_d for GM-1 as determined by plasmon surface resonance (Example 2, Results, page 43). Williams teaches that mice immunized intranasally with wild-type EtxB exhibited high titre serum anti-EtxB IgG antibody levels (titre=5757+/-785) while mice immunized intranasally with mutant EtxB(H57S) exhibited significantly lower anti-EtxB IgG antibody levels (titre=1205+/-222) (Example 3, page 43). Williams teaches that both EtxB(H57S) and CtxB(H57A), when coadministered to mice intranasally with ovalbumin, elicited a reduced anti-ovalbumin immunogenic response in said mice when compared to wild-type EtxB and CtxB (Example 4, page 44).

It is noted that Williams is considered to teach "a method of using a mutant of EtxB or CtxB comprising delivering an agent to a target cell" (claim 1), "wherein the agent is selected from the group consisting of a peptide or protein of interest" (claim 2) because Williams teaches a method comprising contacting mouse CD8+ T-cells with the various CtxB/EtxB mutant proteins. Williams teaches that said CtxB/EtxB mutant proteins bound to said mouse CD8+ T-cells and as such, said CtxB/EtxB mutant proteins were delivered to a target cell (i.e. mouse CD8+ T-cells being the target cell). Further, said CtxB/EtxB mutant proteins are considered to be the agent.

Thus, Willaims *et al.* anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 10-12, 17, 18, 21 stand rejected and newly added claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Williams *et al.* in view of Loregian *et al.*, Marcello, Nashar et al[a] (1993) and Nashar et al[b] (2001).

Applicant notes that Williams *et al.* fails to anticipate as argued above, and summarize and argue each of the additional references separately. More specifically, it is argued that the references fail to teach MHC class I processing, and teach away in part by teaching the use of

other cells and affects of providing EtxB with a variety of antigens. See Applicant's amendment pages 9-11. Applicant's arguments have been fully considered, but not found persuasive.

The teachings of Williams are discussed above. Briefly, Williams teaches that binding of CtxB/EtxB to GM-1 is a critical event that correlates with CtxB/EtxB entry into a target cell (page 2, lines 1-5; page 4, lines 29-30; page 12, lines 20-25; page 14, lines 7-13). Williams teaches that CtxB/EtxB molecules with point mutations within the claimed loop region (i.e. amino acids 45-65) retain GM-1 binding activity but lack other activities, such as immunogenicity and toxicity (page 12, lines 20-25). It is acknowledged that Williams does not teach delivery of a variety of specific antigens fused to CtxB/EtxB mutant proteins. Further, it was acknowledged that Loregian, Marcello, Nashar et al[a] and Nashar et al[b] do not teach mutants of EtxB/CtxB containing mutations in the region spanning amino acid residues E51 to I58, however clearly teach the use of CtxB/EtxB for the delivery of a variety of antigens to a cell. The cited references were provided simply to demonstrate that the use of CtxB/EtxB was well known for delivery of a variety of antigens.

Again, Loregian was cited for the teaching that a peptide corresponding to the 27 C-terminal amino acids of HSV-1 polymerase (POL), when fused to CtxB/EtxB, mediates delivery of the POL portion of a POL-CtxB/EtxB fusion protein into the nucleus of cells when said POL-CtxB/EtxB fusion protein is incubated with said cells (page 5223: col. 1 to col. 2, paragr. 2). Loregian teaches that CtxB/EtxB binding to GM-1 on the surface on target cells mediates internalization and uptake of CtxB/EtxB (page 5221, col. 1, paragr. 2, lines 5-8). Marcello teaches a method of delivery of a peptide into the cytosol of a cell comprising contacting a cell with a CtxB/EtxB protein fused to said peptide (page 8997, col. 2: lines 1-4; paragr. 2, lines 1-6).

Marcello teaches that CtxB/EtxB binding to GM-1 on the surface of target cells mediates internalization and uptake of CtxB/EtxB (page 8997, col. 2, lines 1-4). Marcello also teaches that CtxB/EtxB can enter the intracellular vesicular network (page 8998, col. 1, lines 1-4). Nashar et al[a] teaches the state of the art of EtxB/CtxB as carriers for the oral delivery of heterologous antigens and epitopes. Nashar teaches that EtxB/CtxB are easily manipulated for either genetic or chemical attachment of antigens or epitopes (page 235, col. 2, paragr. 1). Nashar teaches that EtxB/CtxB binding to GM-1 mediates the uptake of EtxB/CtxB into eukaryotic cells (page 236, col. 1, paragr. 1). Nashar teaches that EtxB/CtxB fusion proteins containing proteins of interest to be delivered to a cell can be easily produced in large quantities (page 236, col. 2, paragr. 4 to page 237, col. 1, line 2). Finally, Nashar et al[b] teaches that antigen presenting cells, including B cells and dendritic cells, have GM-1 localized on the cell surface and that said cells can bind EtxB/CtxB (page 544, col. 2, lines 1-13 and see throughout entire document). Nashar teaches that an ovalbumin antigen covalently linked to CtxB/EtxB promotes uptake and immunological response to ovalbumin in said cells. Nashar teaches that CtxB/EtxB binding to GM-1 on the surface on target cells mediates internalization and uptake of CtxB/EtxB (page 549, col. 1, line 1 to paragr. 3).

Loregian, Marcello, Nashar et al[a] and Nashar et al[b] do not teach mutants of EtxB/CtxB containing mutations in the region spanning amino acid residues E51 to I58, however this is the teaching of Williams. As noted in the previous office action, the intended use limitations bear little weight on the determination of patentability because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art. In a claim drawn to a process, the intended use must result in a manipulative difference

as compared to the prior art. See MPEP § 2111.02, *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, since the method steps recited in the claim(s) and the method steps taught by the combined teachings of Williams, Loregian, Marcello, Nashar et al[a] and Nashar et al[b] are the same, practice of the process would inherently result in the same outcome.

Neither Applicant's arguments nor the guidance of the present specification provides the necessary guidance to address this issue, and the great breadth encompassed by the claims. Upon review of the disclosure, it is found that the present specification fails to provide any unexpected results commensurate in scope with the claimed invention.

Conclusions

No claim is allowed.

As indicated previously, an *in vitro* method of delivering a peptide to a cell expressing GM-1 ganglioside receptors on the surface of said cell comprising contacting said cell with a mutant B-subunit of *E. coli* heat labile enterotoxin (EtxB) or a mutant B-subunit of *Vibrio cholerae* cholera toxin (CtxB) covalently linked to said peptide, said mutant EtxB or mutant CtxB comprising one of the following point mutations within the region spanning amino acid residues E51 to I58 of the □4-□2 loop of EtxB or CtxB: CtxB(E51A), CtxB(Q56A), CtxB(H57A) and EtxB(H57S), thereby delivering said peptide into said cell; and a kit comprising said mutant EtxB or mutant CtxB covalently linked to said peptide, would be found allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

Joe Woitach
AU 1632